D2-03 Molecular Targeted Therapy: Biomarkers, Thu, 12:30 - 14:15

Erlotinib (E) as a single agent or intercalated with carboplatin and paclitaxel (ECP) in an EGFR biomarker-selected, previously untreated NSCLC population

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Background: Platinum-based chemotherapy (CT) for previously untreated advanced NSCLC improves survival (OS) and QoL but can have considerable toxicity. Erlotinib (E) (Tarceva®), an oral EGFR inhibitor, improves OS and progression-free survival (PFS) in 2nd- and 3rd-line treatment of NSCLC with acceptable toxicity, similar response and OS to chemotherapy, and a suggestion that pts whose tumors express EGFR might benefit most. In unselected CT-naïve NSCLC pts, adding daily E to concurrent CT did not improve outcome. Preclinical data suggest that intercalating E with CT may be superior to continuous concurrent dosing. This trial was designed to evaluate E alone or E intercalated with CT for front-line treatment in an EGFR-selected population.

Methods: CT-naïve stage IIIB/IV NSCLC pts, ECOG PS 0-2, with EGFR-positive tumors by FISH or IHC were randomized equally to E 150 mg/d or carboplatin AUC 6/paclitaxel 200 mg/m^2 on Day 1 plus E 150 mg/d on Days 2-15 of every 21-day cycle (ECP). After 4 cycles, pts in both arms continued daily E until PD, refusal, unacceptable toxicity, or death. EGFR IHC and FISH testing are performed at the University of Colorado Cancer Center with a planned 5-day or less turnaround. Stratification factors are: number of positive (1 vs. 2) EGFR tests, performance status (0/1 vs. 2), extent of disease (stage IIIB vs. IV), and cigarette smoking status (current vs. former vs. never). The primary study endpoint is disease progression at 6 months. Secondary endpoints include PFS, OS, and response rate. Enrollment goal is 140 pts.

Results: As of February 19, 2007, 66 pts have been randomized (33 E; 33 ECP). Median age is 61 yrs (range, 31-87); 61% are female; 12% Asian; 36% never smokers, 12% current smokers, and 52% former smokers; 94% ECOG PS 0/1; 89% Stage IV; 77% adenocarcinoma. Median EGFR reporting time is 4 days (range, 1-9). 88% of randomized pts' tumors are IHC positive, 53% FISH positive, and 41% are both IHC and FISH positive for EGFR. 123 patients have been screened: 8% of pts' tumors are EGFR IHC and FISH negative and 15% are not sufficient for EGFR testing. Of randomized patients, 12% have EGFR mutations and 11% have KRAS mutations. There are no notable differences in demographics or baseline characteristics between arms with the exception of more females and PS 0 patients in the E arm. Preliminary safety data show no notable differences between treatment arms.

Conclusions: Selection of untreated advanced NSCLC pts for E therapy based on real-time EGFR testing of tumor tissue is feasible. Preliminary evaluation of efficacy and safety data will be presented.

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MERIT: a prospective study of putative relationships between tumour biomarkers and clinical benefit from erlotinib in advanced non-small cell lung cancer (NSCLC)

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Background: Erlotinib (Tarceva®), a potent, orally active inhibitor of EGFR tyrosine kinase, significantly prolonged survival, delayed symptom progression and improved quality of life compared with placebo in patients with relapsed NSCLC (Shepherd et al. NEJM 2005;353:123-132). Exploratory univariate analyses suggested a beneficial effect of erlotinib on survival in patients with EGFR-positive tumours or high *EGFR* gene copy number (Tsao et al. NEJM;353:133-144). In a multivariate analysis, survival on erlotinib was not significantly affected by EGFR expression status, *EGFR* copy number, or *EGFR* mutation status, but relationships between such markers and clinical outcomes on erlotinib have not been prospectively evaluated. The goal of the multicentre, open-label phase II MERIT study was to identify molecular markers that may be predictive for clinical benefit with erlotinib.

Methods: Eligible patients had advanced (stage IIIB/IV) NSCLC, ECOG PS 0-2, were ≥ 18 years old, and had failed ≥ one chemotherapy regimen (or refused/were unsuitable for chemotherapy). An important inclusion criterion was that a tumour biopsy should be performed by bronchoscopy prior to the start of treatment. Erlotinib (150mg/day p.o.) was given until disease progression, death, or unacceptable toxicity. Dose reductions were permitted for adverse events (AEs). Tumour response was assessed every 6 weeks until week 24, then every 12 weeks. Clinical benefit was defined as either an objective response (RECIST), or stable disease ≥ 12 weeks. Safety assessments (laboratory tests and AE recording) were performed at regular intervals. Tumour biopsies were analysed using gene expression profiling on fresh-frozen tissue, and IHC for EGFR and downstream signalling molecules. Receptor mutations were evaluated by DNA sequencing, and gene amplification was assessed using FISH.

Results: 264 patients from 26 centres in 12 countries were available for evaluation of efficacy. Their median age was 61.0 years (range 32–85). Other baseline characteristics were: male, 70%; female 30%; stage IIIB, 26%; stage IV, 74%; ECOG PS 0, 13%; PS 1, 64%; PS 2, 23%; Caucasian, 61%; Oriental, 38%; other, <1%; non-smoker, 27%; ever-smoker, 73% (current, 27%; past, 46%); adenocarcinoma, 41%; squamous-cell carcinoma, 38%; large-cell carcinoma, 5%; other, 17%. 236 patients (89.4%) had previously received chemotherapy (including neo-adjuvant and adjuvant treatment). For most patients in MERIT (130; 49.2%) erlotinib was second-line therapy, but 72 (27.3%) received third-line and 62 (23.5%) first-line erlotinib. 36 patients (13.6%) had an objective response; 83 (31.4%) had clinical benefit. Median overall survival was 7.6 months (95% CI 7-9); median progression-free survival was 11.3 weeks (95% CI 8-12). 226 of 257 patients (87.9%) had at least one AE, and 62 (24.1%) had a serious AE. 193 patients (75.1%) had at least one treatment-related AE and 37.4% had at least one AE ≥ grade (gr) 3. The most common AEs were: rash (61.9%;